first fluorescence-labeled antibody and the intensity of the fluorescence from the second or third fluorescence-labeled antibody;

(6) classifying the neutrophilic cells obtained in step (4) into groups different in degree of maturity on the basis of the intensity of the fluorescence from the second fluorescence-labeled antibody and the intensity of the fluorescence from the third fluorescence-labeled antibody; and

(7) counting the number of cells in each of the groups.

Please add the following new claim:

15. The method of claim 1 wherein the step (2) of removing erythrocytes is performed after the adding step (1).

REMARKS

New claim 15 has been added. Support for this claim may be found at page 11, lines 2-9 of the specification.

Rejection Under 35 U.S.C. § 112, Second Paragraph

The Examiner rejected Claims 1-10 and 12-14 under 35 U.S.C. §112, second paragraph. (Paper No. 15 at 3) asserting that the claims were indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant's amendments adopt the Examiner's suggestions. No new matter has been added. Entry and favorable consideration of these amendments is respectfully requested.

Rejections Under 35 U.S.C. § 103

Claims 1-14 were rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Bowen et al. (Laboratory Hematology, 1997 – hereafter "Bowen") in view of Gopinath et al. (Cytometry, 1997 – hereafter "Gopinath"). Applicant respectfully traverses this rejection for the reasons which follow.

Applicant's have previously stated the threshold standard for a *prima facie* case of obviousness. Before any evidence or even before any speculation as to the skill of ordinary persons in the art, at a minimum, to maintain a *prima facie* rejection based on obviousness, all elements and limitations of the claims must be present in the cited art. In order to establish a *prima facie* case of obviousness, i.e. the cited references must teach every element recited in the claims. *In re Rouffet,* 149 F. 3d 1350; 47 USPQ2d 1453 (Fed. Cir., 1998). All properties and attributes must be considered by the Examiner. *In re Antonie*, 195 USPQ6 (CCPA 1977).

Bowen has been cited during this prosecution to support at least three separate rejections of Claim 1 (among other claims). Each time in response, Applicants have demonstrated Bowen to be inadequate as a citation because it fails to account for all claimed elements and limitations of Claim 1 (as well as the other claims dependent therefrom). Now the Examiner has returned with yet another citation of Bowen, this time in combination, to support another rejection. Bowen is no less inadequate for the present form of the rejection.

To support the citation of Bowen, the Examiner states:

> "Bowen teach(es) that simultaneous quantitation of SALS and fluorescent labeled monoclonal antibody binding to CD45, CD16, and CD11b define highly reproducible developmental maturation patterns of the granulocytic cell population series in flow cytometry." (Paper 15, p. 5)

Even assuming this broad statement of Bowen's teachings is supportable (though no supporting evidence is apparent), this is not what Applicants' claims recite. Applicant claims, in part:

> (5) distinguishing eosinophils and neutrophilic cells in the granulocytic cells obtained in step (4) on the basis of the intensity of the fluorescence from the first fluorescence-labeled antibody and the intensity of the fluorescence from the second or third fluorescence-labeled antibody;
>
> (6) classifying the neutrophilic cells obtained in step (4)] into groups] different in degree of maturity on the basis of the intensity of the fluorescence from the second fluorescence-labeled antibody and the intensity of the fluorescence from the third fluorescence-labeled antibody; and
>
> (7) counting the number of cells in each of the groups.

Clearly, the Examiner does not, indeed cannot, account for the specific elements and limitations of Claim 1 in Bowen. There is no example or disclosure in Bowen where eosinophils are distinguished and classified, as provided by the above limitations of Claim 1. Nor can the Examiner point to any disclosure in Bowen that teaches, suggests or motivates combination with another method that does disclose this. This dooms the rejection.

Yet, and surprisingly, given the citation of Gopinath, the Examiner acknowledges that Bowen is fatally deficient, e.g., "Bowen differ(s) from the instant invention in failing to teach distinguishing eosiuophils and neutrophilic cells measured in ... Claim 1." (Paper 15, p. 5, emphasis added.) In addition, the Examiner never points to where Bowen it discloses that neutrophilic cells are classified into different groups maturation on the basis of anti-CD16 and anti-CD11b fluorescence intensity. Naturally, counting the number of cells in groups not taught by Bowen likewise is absent from the citation.

To fill this acknowledged gap, the Examiner combines Gopinath. The abstract of Gopinath, however, states "Here we describe a simple, single-step method for definition of eosinophils utilizing their high side scatter and CD16 fluorescence negativity to distinguish them from neutrophils." (Gopinath Abstract) Gopinath's technique of discrimination, therefore, uses side scattered light and CD16 (a "second antibody," using Applicant's claim parlance).

Comparing this with Claim 1, wherein eosinophils are distinguished based on fluorescence (not scattered light) of the first antibody and the second or third antibody. Clearly Gopinath fills no gap in Bowen, it widens it. Even if Bowen's teachings regarding use of CD11b were applicable to Gopinath (and no evidence shows that they are) and CD11b were "more useful" than CD16, as the Examiner alleges, this does not teach Applicants' claim, i.e., distinguishing eosinophils without scattered light. The combination of Bowen and Gopinath simply does not account for using the first and second (or third) antibodies to distinguish eosinophils.

As Applicants have stated so often in response, to support the various §102 and §103 rejection asserted, the citations must account for all claimed elements and limitations. They are not merely springboards for speculation by the Examiner. Yet, and once again, speculation and conjecture is exactly all that supports the rejection. Facts fail it. And it is well settled that a rejection under § 103 must be supported by facts. *Ex parte Saceman*, 25 U.S.P.Q.2d 1472 (BPAI 1993). Where it is not based on facts, it cannot stand. *Ex parte Porter,* 25 U.S.P.Q.2d 1144 (BPAI 1992). This rejection, as with various others based previously on Bowen, cannot stand.

Based on such unstable foundation, the Examiner's pronouncements as to the level of skill in the art to combine Bowen and Gopinath are, frankly, irrelevant. Considering

these for purposes of argument, however, these are equally vacant. As has been demonstrated, incorporating the teaching of Gopinath into the method of Bowen does not arrive at Applicants' claimed elements and limitations. There is no motivation, teaching or suggestion to go beyond the teaching of Bowen, let alone of both Gopinath and Bowen, save for the Examiner's expecctation that there should be. This is clear in the proscriptive nature of the Examiner's unsupported explanation as to motivation:

> "It would have been obvious to one of ordinary skill in the art at the time of the instant invention to incorporate the teaching of Gopinath in distinguishing between neturophils and eosinophil populations, with the flow cytometric method of Bowen because Gopinath specifically taught that a combination of side angle scatter and CD16 flouresence intensity measurement provides for an accurate isolation of eosinophils from neutrophils in the granulocytic populations taught in the method of Bowen and Bowen further taught that CD11b expression appears earlier and prior to the expression of CD16; therefore, CD11b is more useful in defining granulocytes in early maturation stages than CD16."

Paper No. 15, page 6.

Reference to Applicants' claim limitations appear nowhere in this analysis of obviousness. Applicants are frankly at a loss as to exactly what the Examiner is trying to demonstrate to be obvious, given this lack of reference to Applicants claims and their limitations. The question is not whether Bowen and Gopinath can be combined, but whether it can be shown that the proposed combination 1) meets Applicants claims and 2) is motivated. The Examiner has not answered these questions. Applicants submit she cannot. General statements as to the state of the art do not support the rejection, especially those not tied to the particular claims. Moreover, the mere level of skill in the art cannot be relied upon to provide the motivation to combine references, *Al-Site Corp., v. VSI Int't Inc.*, 174 F.3d 1308 (Fed. Cir. 1999); that is, even if the references did encompass all claimed elements and limitations--here they do not.

Further spurious combinations, unfounded rationales and unsupported conjecture regarding Bowen should cease. Bowen has been considered and reconsidered, and the Examiner's own actions in mixing and matching rejections only demonstrate Applicants' position and the patentability of Applicants' claims over Bowen. As has been repeatedly argued from the outset of prosecution, the Examiner should reconsider and allow all claims.

In view of the above, reconsideration and withdrawal of this rejection is respectfully requested.

Conclusion

For the reasons set forth above, entry of the amendments, reconsideration, and allowance of the claims respectfully is requested. If the Examiner has any questions regarding this paper, please contact the undersigned attorney.

I hereby certify that this correspondence is being deposited with sufficient postage to the United States Postal Service as first class mail in an envelope addressed to: Commissioner for Patents, Washington, D.C. 20231, on April 2, 2003
(Date of Deposit) Charles T. J. Weigell
Name of applicant, assignee, or Registered Representative
Signature
4/2/02
Date of Signature

Respectfully submitted,

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EXHIBIT 1

"MARKED UP"

1. A method for classifying and counting leukocytes comprising the steps of:

(1) adding to a hematological sample the following fluorescence-labeled antibodies labeled with fluorescent dyes which emit fluorescences distinguishable from each other:

(a) a first fluorescence-labeled antibody which binds specifically to leukocytes,

(b) a second fluorescence-labeled antibody which binds to at least one kind of neutrophilic cells, and

(c) a third fluorescence-labeled antibody which binds to at least one kind of immature granulocytic cells,

in order to stain the leucocytic cells in the hematological sample;

(2) removing erythrocytes from the hematological sample;

[(2)] (3) analyzing the resulting hematological sample using a flow cytometer to measure at least one scattered light signal and three separate fluorescence signals;

[(3)] (4) classifying granulocytic cells on the basis of intensity of the scattered light and intensity of fluorescence from the first fluorescence-labeled antibody;

[(4)] (5) distinguishing eosinophils and neutrophilic cells in the granulocytic cells obtained in step (4) on the basis of the intensity of the fluorescence from the

first fluorescence-labeled antibody and the intensity of the fluorescence from the second or third fluorescence-labeled antibody;

[(5)] (6) classifying the neutrophilic cells obtained in step (4) [intro groups having different degrees of maturity] into groups [of neutrophilic cells] different in degree of maturity on the basis of the intensity of the fluorescence from the second fluorescence-labeled antibody and the intensity of the fluorescence from the third fluorescence-labeled antibody; and

[(6)] (7) counting the number of cells in each of the groupes.